Long-term follow-up of patients with early atherosclerosis

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Purpose: **Patients with premature peripheral vascular disease may respond differently than their older counterparts. To determine the impact of early onset of atherosclerosis on outcome, we decided to compare a group of these patients with a group of patients with typical onset of atherosclerosis with regard to early complications, indications for intervention, site of disease at initial presentation (aortoiliac, infrainguinal, or cerebrovascular), and long-term outcomes (secondary revascularization, amputation, and death).**
Method: **All patients younger than 50 years old requiring operative intervention between 1987 and 1992 were retrospectively compared with a group of patients greater than 60 years old, randomly selected from patients who underwent operation during the same time period. Patients were evaluated and compared for indications, risk factors, and early and late outcomes.**
Results: **Patients with early onset atherosclerosis at the aortoiliac or infrainguinal level had a higher late amputation rate (17% versus 3.9%, $p = 0.02$) and poorer overall outcome than their older cohorts. Patients with cerebrovascular disease in both cohorts had similarly good prognoses.**
Conclusion: **Aortoiliac or infrainguinal disease diagnosed in patients less than 50 years of age portends a poorer outcome than does similar disease in an older patient population.**
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Atherosclerosis is typically thought of as a disease process of the elderly population. However, a subgroup of patients are diagnosed early, before the age of 50, with significant occlusive disease. The factors responsible for this premature atherosclerosis are not well delineated but have become an area of increasing interest over recent years. Young patients may not respond in the same way that their older counterparts do to various surgical interventions. The outcome of these patients has been suggested to be worse than their older counterparts. To further evaluate the impact of premature atherosclerosis on long-term outcome, we decided to study the early complications and long-term need for subsequent revascularization, amputation, and late death in a group of these patients. We also evaluated the impact of the site of initial disease presentation on long-term outcomes.

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METHODS

A retrospective review of all patients under 50 years of age who underwent operative intervention for vascular occlusive disease between 1987 and 1992 was undertaken. A group of patients over 60 years of age, with the same disease distribution as the younger patients (determined by level of operation, angiograms, and noninvasive study results), served as control subjects. Control subjects were randomly selected from patients greater than 60 years of age who underwent operative intervention by the same surgeons during the same time period as patients with premature peripheral vascular disease (PVD). Patient charts were examined for indications for operation, procedures performed, complications, bypass patency rates, subsequent operations, early and late major amputations, early and late mortality rates, and risk factors. Risk factors evaluated included history of smoking, diabetes mellitus, sex, hypertension, coronary artery disease, and other medical comorbidities. Patients with aneurysmal disease, trauma, or other

nonocclusive arterial disorders were excluded from the study. Young patients were compared with reference to location of initial disease at presentation, history of smoking, diabetes, and sex. Young and old patients were evaluated with regard to overall outcome (death, amputation, graft failure, cerebrovascular accident, myocardial infarction, or recurrent symptoms), mortality rate, amputation, and the need for reoperation. Patients were divided into three groups on the basis of the initial site of intervention: A, aortoiliac; B, infrainguinal; and C, cerebrovascular. Patients with cerebrovascular disease were evaluated separately for risk factors, demographics, and outcomes. Patients were considered smokers if they were currently smoking or had quit smoking within the previous 2 years. Coronary artery disease was considered to be present with current or historical evidence of congestive heart failure, ongoing angina, myocardial infarction, or previous coronary artery bypass grafting. Statistical analysis was by chi-squared, multiple linear regression, stepwise logistic regression, and life-table analysis. Significance was taken at the $p < 0.05$ level. Data are expressed with standard deviation.

RESULTS

A total of 76 young patients and 76 control subjects (age >60 years at first operation) were evaluated. There were 29 patients in group A, 26 patients in group B, and 21 patients in group C in both young and old cohorts. Patients in the older cohort were specifically chosen to match the distribution of disease found in the study group. In patients with premature atherosclerosis, mean follow-up was 62 ± 48 months. In the older cohort of patients, mean follow-up was 33.4 ± 27 months. Demographic data on the two groups are presented in Table I. As expected, the study group was significantly younger at the time of their initial surgery than were the control subjects (43.7 ± 5.1 years versus 69.7 ± 6.4 years, $p < 0.0001$). There was not a statistically significant difference in hypertension , or diabetes between the two groups, although juvenile-onset diabetes was more frequent in patients with premature PVD. History of smoking was significantly more common in the younger patients (91% versus 69%, $p < 0.05$). Younger patients also were more often men and more frequently underwent operation for limb salvage (85% versus 60%, $p < 0.05$). In contrast, symptomatic coronary artery disease was more prevalent in the older cohort (60% versus 29%, $p < 0.005$). Five percent of older patients had multilevel disease at time of presentation, as compared to 11.8% of younger patients.

There were no perioperative deaths in the study group nor in the older group. The 5-year mortality rate by life-table analysis was slightly increased in the study group, but this did not achieve statistical significance (26% versus 16.7%, p = NS, 10% confidence intervals). However, when compared with the expected survival rate by the United States National Center for Health Stats Vital Statistics,[1] patients with premature PVD experience a significantly greater mortality rate (26% vs 1.73%, $p < 0.0001$) than expected, whereas older patients only have a minimally increased mortality rate (16.7% vs. 15.04%, p = NS) when compared to the overall population. Early amputation was also more common, although not statistically significant, in the younger patients with PVD (groups A and B), than in their corresponding control subjects (11.5% versus 2.6%, p = NS), whereas late amputation rates, by life-table analysis, were significantly increased in the younger patients (39.5% versus 8.3%, $p = 0.005$, 10% confidence intervals). This is consistent with the higher incidence of limb salvage procedures in the young patients. However, even when older patients initially underwent intervention for limb salvage, only 9.1% eventually required amputations. Secondary procedures were required in about half of the patients in both study groups and in control subjects and were performed for progression of disease rather than graft failure in the vast majority (91%) of patients. Overall poor outcome was significantly increased in the study group (39.5% versus 23.7%, $p = 0.05$).

Factors influencing late outcome

Sex, history of smoking, hypertension, and a history of coronary artery disease did not influence the need for late amputation, secondary revascularization, or late death (Table II). Diabetes was significantly associated with the need for multiple interventions ($p < 0.05$), late amputation (38% versus 14%, $p < 0.02$), and death (25% versus 8%, $p < 0.02$) in patients with premature atherosclerosis but not in the older cohort with typical onset atherosclerosis. Eleven patients in the young cohort had juvenile-onset diabetes, and eight were insulin dependent. Eleven patients in the older cohort had insulin-dependent diabetes. Patients with juvenile-onset diabetes did not have a significantly higher rate of multiple interventions (36%), amputations (27%), or deaths (18%) than did patients with adult-onset diabetes.

Multiple interventions significantly increased late

Table I. Demographics of young and old patients with lower extremity PVD

	Young patients	*Old patients*	*Significance*
Hypertension	23 (42%)	29 (53%)	NS
CAD	16 (29%)	33 (60%)	0.005
Smoking	50 (91%)	38 (69%)	0.01
Diabetes	19 (35%)	20 (36%)	NS
Male sex	47 (85%)	34 (62%)	0.01
Operation for limb salvage	47 (85.5%)	36 (66%)	0.013

CAD, Coronary artery disease.

Table II. Factors influencing late complications in young patients

	Late mortality rate	*Overall amputation rate*	*Revascularization*
Hypertension	6/40 (15%)	8/40 (20%)	11/40 (27.5%)
History of smoking	5/69 (7.2%)	13/69 (18.8%)	19/69* (27.5%)
Male sex	6/62 (9.7%)	12/62 (19.4%)	18/62 (29%)
Diabetes	6/24* (25%)	9/24† (37.5%)	10/24 (41.7%)
Infrainguinal disease	4/26 (15.4%)	11/26* (42.3%)	19/26‡ (73.1%)
Total	8	15	21

*$p < 0.05$.
†$p < 0.006$.
‡$p < 0.0001$.

morbidity and mortality rates. Twenty-one young patients underwent multiple procedures. When young patients required multiple revascularizations for limb salvage, eventual amputation occurred in 41.7%, compared with 13.5% ($p = 0.014$) of patients not requiring multiple interventions. The late mortality rate was also increased in individuals undergoing multiple procedures, with a 33% versus a 6% mortality rate with single interventions. Mean follow-up was significantly longer in patients undergoing multiple procedures (62.2 months vs 40.5 months), as would be expected. However, in most patients who experienced complications, the complication developed within 2 to 3 years after the initial intervention, well within the average follow-up. The mean time to complication or death was less than 30 months in both groups.

Location of initial disease was also related to outcome (Table III). Patients who initially were diagnosed with infrainguinal disease were more likely to require additional procedures in both young and old cohorts. In the younger patients, infrainguinal disease was also associated with a higher late amputation rate and a poorer long-term outcome than either aortoiliac or cerebrovascular disease.

Patients with cerebrovascular disease did similarly well in both young and old cohorts. Both young and old patients with cerebrovascular disease had a similar incidence of symptomatic disease, 57% for older patients and 62% for younger patients. Secondary procedures were required in only 14.3% of young patients and 9.5% of old patients (p = NS). Reoperation was performed as a result of recurrent stenosis in only one (4.8%) of the older cohort and in none of the younger patients. There were no early strokes in either group, with only one young patient having a late cerebrovascular accident. Only one patient who was diagnosed with cerebrovascular disease died during the 5-year follow-up in both cohorts.

DISCUSSION

The clinical profile of a young patient with atherosclerosis is a man with a history of smoking. The incidence of diabetes and hypertension is similar to that in later onset atherosclerosis. Fourteen percent of our young patients had juvenile-onset diabetes. In our experience, diabetes and smoking are a particularly virulent combination. It was of great interest that symptoms of coronary atherosclerosis was seen in only 29% of young patients, despite the advanced nature of the atherosclerosis in the peripheral and cerebral vascular beds. The markedly increased mortality rate in young patients of age-adjusted mortality statistics points out the poor prognosis for this patient group.[1] Although we have no proof of subclinical cardiac ischemia in these young patients, routine cardiac screening for occult disease is an area in need of investigation.

History of smoking was significantly more common in patients with premature atherosclerosis, whereas symptomatic coronary artery disease was more frequently identified in older patients. History of smoking was found to be a significant risk factor for

Table III. Life-table analysis of late outcome (5-year) related to disease location

	Aortoiliac		*Infrainguinal*		*Significance (p)*	
Late factors	*Young*	*Old*	*Young*	*Old*	*Young*	*Old*
Secondary vascular reconstructions	19.2%	50.5%	79%	49%	$p < 0.0001$	NS
Major amputations	37.6%	6.25%	43.1%	11.35%	NS	NS
5-year mortality rate	18.2%	15.66%	27.7%	20%	NS	NS

multiple interventions. Although we were unable to show history of smoking as a major risk factor in amputation or death, this may be due to the high prevalence of smoking in patients with premature atherosclerosis, leaving a very small group of nonsmokers for comparison. Smoking has been identified as a significant risk factor in all major studies of premature atherosclerotic disease.[2-12] The exact mechanism by which smoking impacts on these individuals and why certain individuals seem to be more susceptible to the deleterious effects of smoking is not fully understood.[13] Smoking is known to have an impact on the cholesterol metabolism, including a reduction of plasma high-density lipoprotein levels,[14] as well as to directly affect the vascular endothelial and smooth muscle cells.[15] Smoking is also known to increase plasma fibrinogen levels.[16] Furthermore, smoking is associated with an increased rate of graft failure.[17,18]

Hypertension was most common in patients requiring cerebrovascular reconstructions. Hypertension has not been found to be as prevalent in patients with early onset atherosclerosis, occurring in 6% to 63%, when compared with patients with typical onset atherosclerosis.[2-12,19,20] In our series, hypertension was equally prevalent in both age groups.

Diabetes was present in about one third of both young and old patients with PVD. Patients with diabetes were admitted more frequently with distal, infrainguinal disease and less commonly with cerebrovascular disease. Young patients with diabetes also showed increased rates of early and late major amputation and late mortality. Diabetes is also known to impact adversely on the lipid metabolism[21] and, in combination with smoking, may provide a particularly detrimental environment.

The presence of risk factors that might predispose some individuals to premature atherosclerosis has been a subject of increasing interest over recent years. In our series at least one major risk factor was present in 97% of all patients, and multiple risk factors were present in 67% of patients.

An increased rate of amputation, ranging from 8% to 71% after intervention for PVD, has frequently been identified in patients with early onset atherosclerosis.[4-6,22,23] Late mortality rates have also been increased with 5-year mortality rates of 6.6% to 20%.[2,3,6-8,19,20] Whereas the 5-year survival rate by life-table analysis was similar in both groups, this needs to be taken in the context of the increased age and increased rate of coronary artery disease in the older control group. Age-adjusted mortality rates suggest a marked increase in deaths for the younger atherosclerotic population versus only a minimal decrease in life expectancy for patients with typical-onset atherosclerosis. Most of these deaths are attributed to heart-related or other vascular complications. We have found that patients with premature PVD fare significantly worse than their older cohorts with regard to increased rates of reoperation for limb salvage, ($p < 0.05$), late amputation, ($p < 0.02$), and overall poor long-term outcomes, ($p < 0.05$).

Young patients in our series were diagnosed with a wide array of vascular lesions fairly evenly distributed among cerebrovascular, aortoiliac, and distal disease locations. The presence of cerebrovascular disease in the young patient has not been noted in prior reports. The impact of the initial location of disease presentation on late outcome has not previously been evaluated. In our series, the presence of aortoiliac or lower extremity disease implied significantly different outcomes than does the presence of premature cerebrovascular occlusive disease. Our series does differ from most of those in the literature in that 85% of our patients with premature atherosclerosis underwent operation for limb-threatening disease, whereas most patients (60% to 83%) with premature atherosclerosis presented in most series undergo intervention for claudication.[5,6,10,19] In our patients, initial presentation with infrainguinal disease significantly increased the need for subsequent revascularizations and the risk of amputation. Poor long-term outcome is common in these patients with the early onset of distal disease. We have found that the outlook for patients diagnosed with aortoiliac occlusive disease is also poor, with more than half of the patients requiring

multiple procedures, 20.7% requiring major amputations, and a 17.2% 5-year mortality rate.

In our series, cerebrovascular lesions were associated with a more benign course. Patients with early-onset cerebrovascular disease did not differ from typical onset cerebrovascular disease in their long-term outcome. Secondary procedures were required in only 14.3% of young patients and 9.5% of older patients, with only one patient having development of recurrent cerebral symptoms and restenosis. Only one patient (4.7%) died during the 5-year follow-up in both the young and old cohorts with initial presentation with cerebrovascular disease. Patients with cerebrovascular occlusive disease as the presenting sign of premature atherosclerosis can safely undergo operation with good long-term results. The reasons for these differences in outcome by disease distribution is unclear. We did find a lower incidence of diabetes in our young patients with cerebrovascular disease. Diabetes is associated with increased lipid abnormalities and decreased longevity and was a major determinant of poor outcome in our series. Lipid data were not uniformly available in the retrospective review, and therefore no conclusion on the impact of lipid abnormalities could be drawn.

A prospective study of patients with early atherosclerosis in different disease distributions is needed to elucidate the differences in outcome and perhaps to identify individuals at higher risk for poor long-term survival. Certainly, the control of modifiable risk factors may be very important in the long-term prognosis of individuals with lower extremity disease and aortoiliac disease. Intense investigation into risk factor modification analysis and control of hypercholesterolemia, hypertriglyceridemia, elevated oxidized lipids, and hypercoagulable states is needed if we are to improve on the dismal outcomes in this group of patients.

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DISCUSSION

Dr. Daniel B. Walsh (Lebanon, N.H.). Dr. Harris and colleagues have brought us data demonstrating that young patients with diabetes undergo early and late amputation and die at greater rates than a comparable group of older patients. Smoking is also a likely predictor of poor outcome in these young patients. However, this series was so dominated by patients with a history of smoking that demonstration of smoking as an independent predictor was not possible. Finally, young patients with lower extremity symptoms, whether caused by infrainguinal or aortoiliac disease, had poor and complicated long-term outcomes. These findings are similar to those reported in the past by groups from Texas and South Carolina. To any experienced vascular surgeon they seem intuitively correct.

The issue with regard to cause of these poor outcomes in this younger patient group requires closer examination. In a Cleveland Clinic series of patients with lower extremity disease, only 13% of their patients had normal lipid or lipoprotein profiles. Can you give us some insight into the lipid status of your young patient group? Several investigators have found a high incidence of antiphospholipid syndrome among younger patients with arterial disease. There are also abundant reports of natural anticoagulant or fibrinolytic deficiencies in younger patients with vascular disease, particularly problems with antithrombin III, protein C, protein S, heparin cofactor II, apolipoprotein B, and very low density lipoprotein. Have you any data regarding these abnormalities in your patient group?

Another interesting observation was that of Valentine et al., who found that arterial size, particularly small aortic size, was a significant predictor of poor outcome. Can you give us any insight into the relative sizes of the aortoiliac and infrainguinal arteries involved between your younger and older groups of patients with atherosclerosis?

Dr. Linda M. Harris. Unfortunately, we did not have a chance to evaluate the size of the aorta or the vessels and compare the two groups, so we don't know whether there was any significant difference in vessel size.

With regard to the first question, we did look at a subset of these patients. Unfortunately, because it was a retrospective study, we did not have complete lipid data on all of the patients. We did obtain hypercoagulable and lipid data on a subgroup of patients who were still available for analysis.

When we looked at this subgroup, we found that the routine lipid profiles were only minimally elevated from a control group. So if you examined the younger patients, their normal cholesterol, high-density lipoprotein and low-density lipoprotein levels were not markedly different, although they were slightly elevated (in the 200 to 220 range). However, we also looked at oxidized lipids and found that these were markedly increased in the younger age population compared with both control subjects of similar age and with patients with older onset of atherosclerosis.

We also looked at hypercoagulable states in this subgroup and only found them to be present in about 13% to 20% of patients. I understand that there are some groups that seem to find it to be a more prevalent problem. We did not study platelet abnormalities, and we didn't study homocystinuria, but we did look at the most typical hypercoagulable states, including deficiency in protein C, protein S, antithrombin III, and a few other factors. We do think that these younger patients need to be aggressively treated for whatever hypercoagulable or lipid abnormalities that they do have. We are currently prospectively studying these younger patients to determine what we can modify to possibly improve their dismal outcomes.